Biomedicine & Pharmacotherapy 171 (2024) 116055

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Deaths induced by compassionate use of hydroxychloroquine during the first COVID-19 wave: an estimate

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ARTICLE INFO

Keywords:
Covid-19
Off-label treatment
Safety
Repurposing

ABSTRACT

Background: During the first wave of COVID-19, hydroxychloroquine (HCQ) was used off-label despite the absence of evidence documenting its clinical benefits. Since then, a meta-analysis of randomised trials showed that HCQ use was associated with an 11% increase in the mortality rate. We aimed to estimate the number of HCQ-related deaths worldwide.

Methods and findings: We estimated the worldwide in-hospital mortality attributable to HCQ use by combining the mortality rate, HCQ exposure, number of hospitalised patients, and the increased relative risk of death with HCQ. The mortality rate in hospitalised patients for each country was calculated using pooled prevalence estimated by a meta-analysis of published cohorts. The HCQ exposure was estimated using median and extreme estimates from the same systematic review. The number of hospitalised patients during the first wave was extracted from dedicated databases. The systematic review included 44 cohort studies (Belgium: k = 1, France: k = 2, Italy: k = 12, Spain: k = 6, Turkey: k = 3, USA: k = 20). HCQ prescription rates varied greatly from one country to another (range 16–84%). Overall, using median estimates of HCQ use in each country, we estimated that 16,990 HCQ-related in-hospital deaths (range 6267–19256) occurred in the countries with available data. The median number of HCQ-related deaths in Belgium, Turkey, France, Italy, Spain, and the USA was 240 (range not estimable), 95 (range 92–128), 199 (range not estimable), 1822 (range 1170–2063), 1895 (range 1475–2094) and 12739 (3244− 15570), respectively.

Conclusions: Although our estimates are limited by their imprecision, these findings illustrate the hazard of drug repurposing with low-level evidence.

1. Introduction

In December 2019, a new virus emerged in Wuhan, located in Hubei Province, China: [1] the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for the Coronavirus disease 2019 (COVID-19). This RNA-positive virus has caused a global pandemic. As of 2nd April 2023, there were 764474387 confirmed cases of COVID-19 worldwide and 6915286 deaths [2].

Many treatments have been repurposed with varying degrees of success for patients, such as dexamethasone [3], hydroxychloroquine (HCQ) [4,5], remdesivir [4,6], or a combination of lopinavir and ritonavir [4,7], based on their effectiveness against other pathogens with similar structure or mechanism of action to SARS-CoV-2. For instance, remdesivir and lopinavir/ritonavir, which are prodrugs that form an analogue of adenosine triphosphate and inhibit viral RNA polymerase and replication, inhibit human and animal coronaviruses in vitro [8,9]. HCQ, a 4-aminoquinoline drug used to treat malaria and autoimmune rheumatic diseases, inhibits viral replication by increasing the pH of the

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https://doi.org/10.1016/j.biopha.2023.116055
Received 7 September 2023; Received in revised form 11 December 2023; Accepted 21 December 2023
Available online 2 January 2024
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endosome used for cell entry. In addition, HCQ may interfere with angiotensin-converting–enzyme 2 glycosylation, which is the cellular receptor of SARS-CoV-2 [10,11]. During the first wave of the pandemics, off-label use of HCQ has been proposed as a treatment option for COVID-19. Subsequent studies documented however an unfavourable risk-benefit balance, including the RECOVERY trial that showed a significant increase in cardiac mortality as well as a trend for increased all-cause mortality risk with HCQ [5]. In a meta-analysis of 14 trials testing HCQ in hospitalised patients with various doses, HCQ was associated with an 11% (95%CI 2–20%) increase in all-cause mortality [12].

The main objective of our study was to estimate the mortality attributed to compassionate use of HCQ in the context of COVID-19 before the publication of reliable randomised controlled trials (RCTs).

2. Methods

2.1. Outcomes

The main outcome was the estimated number of excess deaths amongst hospitalised patients for COVID-19 during the first wave of the pandemic attributable to HCQ worldwide.

2.2. Sources of data

2.2.1. Mortality rates and HCQ exposure

We conducted a systematic review and a meta-analysis of cohort studies to estimate the mortality rates and the proportion of HCQ exposure in hospitalised patients in each country represented in the available studies. We conducted a literature search to identify all published studies reporting the number of patients on all treatments examined in COVID-19. We searched Pubmed, from 1st December 2019, to 15th March 2021, using the keywords "coronavirus", "severe acute respiratory syndrome 2 coronavirus", "SARS-CoV-2", "novel coronavirus", "nCoV", "2019-nCoV" and "COVID-19" and "cohort". From Pubmed, we selected studies according to the following inclusion criteria: multicentre study, study size $\geq$ 500 patients to avoid centre effect, study reporting the treatments used in COVID-19 and the number of patients treated with these drugs. Studies including only patients receiving HCQ, receiving HCQ from August 2020 onwards, and patients already treated with HCQ for autoimmune conditions were excluded, as well as studies from countries for which mortality data were lacking. Two authors (AP and JCL) reviewed the titles, abstracts and full texts of all articles. If there was any doubt, a third reviewer (SM) made the final decision. When different studies were grouped in an article, we verified whether the studies had already been individually selected and if so, they were removed from our study. We did not consider studies containing only ICU patients because too many external parameters could influence the results. From the selected studies, two authors (AP and SM) independently extracted the type of study, inclusion dates, mortality rates, percentages of ICU admissions, countries of study, and the number of patients receiving HCQ. We contacted the authors of the included studies in case we needed additional data.

2.2.2. Hospitalisation

We obtained the total number of hospitalisations by country from the dedicated databases [13–15]. We used hospitalisation data from the beginning of the pandemic in each country (mostly from March 2020 onward) until 17th July 2020 (i.e. date of publication of the RECOVERY trial[5]).

2.2.3. Relative HCQ effect on death

We used the odds ratio (OR) for HCQ-related mortality estimated from a previous meta-analysis of RCTs (i.e. OR=1.11) [12].

2.3. Statistical analysis

2.3.1. Mortality rates and HCQ exposure

The mortality rates for each country were estimated using a meta-analytic approach by pooling (random-effects model) the proportions reported in all included cohort studies. The HCQ exposure was estimated using median and extreme estimates from the same systematic review. A sensitive analysis was conducted using the estimate of mortality rate in hospitalised patients from other sources such as national surveillance report and regionwide analysis.

2.3.2. Number of excess deaths attributable to HCQ

We calculated the number of deaths in hospitalised patients ($N_{hospitalised\ patients}$) by multiplying the number of hospitalised patients receiving HCQ by the mortality rate of each country. The number of deaths (N_{deaths}) related to HCQ exposure was obtained by multiplying (i) the previously estimated number of in-hospital deaths per country and (ii) the OR of HCQ-related mortality. The main source of uncertainty included in the model was the range of HCQ exposure, which was estimated using the median and extreme values (minimum, maximum) reported in the included cohort studies:

$$N_{death} = N_{hospitalised\ patients} \times \text{mortality rate} \times \text{HCQ exposure}_{median,\ min,\ max} \times OR_{HCQ\text{-}mortality}$$

We performed statistical analysis with R (meta-package, *R Language and Environment for Statistical Computing, Vienna, Austria*).

3. Results

3.1. Study characteristics

We retrieved 7848 articles using the previously mentioned search terms. After reviewing titles, abstracts, and some full texts, we selected 44 studies totalizing 98406 patients (Fig. 1). The 44 included studies were conducted in Turkey (k = 3) [16–18], Belgium (k = 1) [19], France (k = 2) [20,21], Spain (k = 6) [22–27], Italy (k = 12) [28–39], and the USA (k = 20) [40–59] (Table 1). Out of the 44 studies, 5 studies were used only to estimate in-hospital all-cause mortality [21,29,39,58,59]. Among the 44 studies, 5 (11%) were prospective [20,22,32,38,43] and 32 (72%) included consecutive patients [16–18,20,22,24–28,30–32,34–36,41,42,44,45,47–54,56,57] (Table 1). The median number of patients included in each study was 1109 (range 348–15111), including 20% admitted to the ICU (range 0–68). The median age of the patients was 65 years (range 56–75), and 58% were men (range 47–96). The all-cause mortality was 21% (range 9–34%). Eleven studies (25%) were designed to report the treatment effect of compassionate drug use [19,22,23,28,39,46–48,55,58,59].

3.2. HCQ exposure, mortality rates and HCQ-related deaths

The number of patients treated with HCQ for COVID-19 for each country ranged from 10,018 to 551,417, with a heterogeneous exposure varying from 16% (France) to 84% (Spain). The mortality rates were calculated using data from one (Belgium) [19] to 20 cohorts (USA) (Fig. 2) [40–59]. The all-cause mortality of in-hospital patients ranged from 6% (Turkey) to 23% (Italy) (Table 2).

The median number of HCQ-related deaths in Belgium, Turkey, France, Italy, Spain, and the USA was 240 (range not estimable), 95 (range 92–128), 199 (range not estimable), 1822 (range 1170–2063), 1895 (range 1475–2094) and 12,739 (range 3244–15570), respectively. Overall, using median estimates of HCQ use in each country, we estimated that 16,990 HCQ-related in-hospital deaths (range 6420–20294) occurred in the countries with available data Table 3.

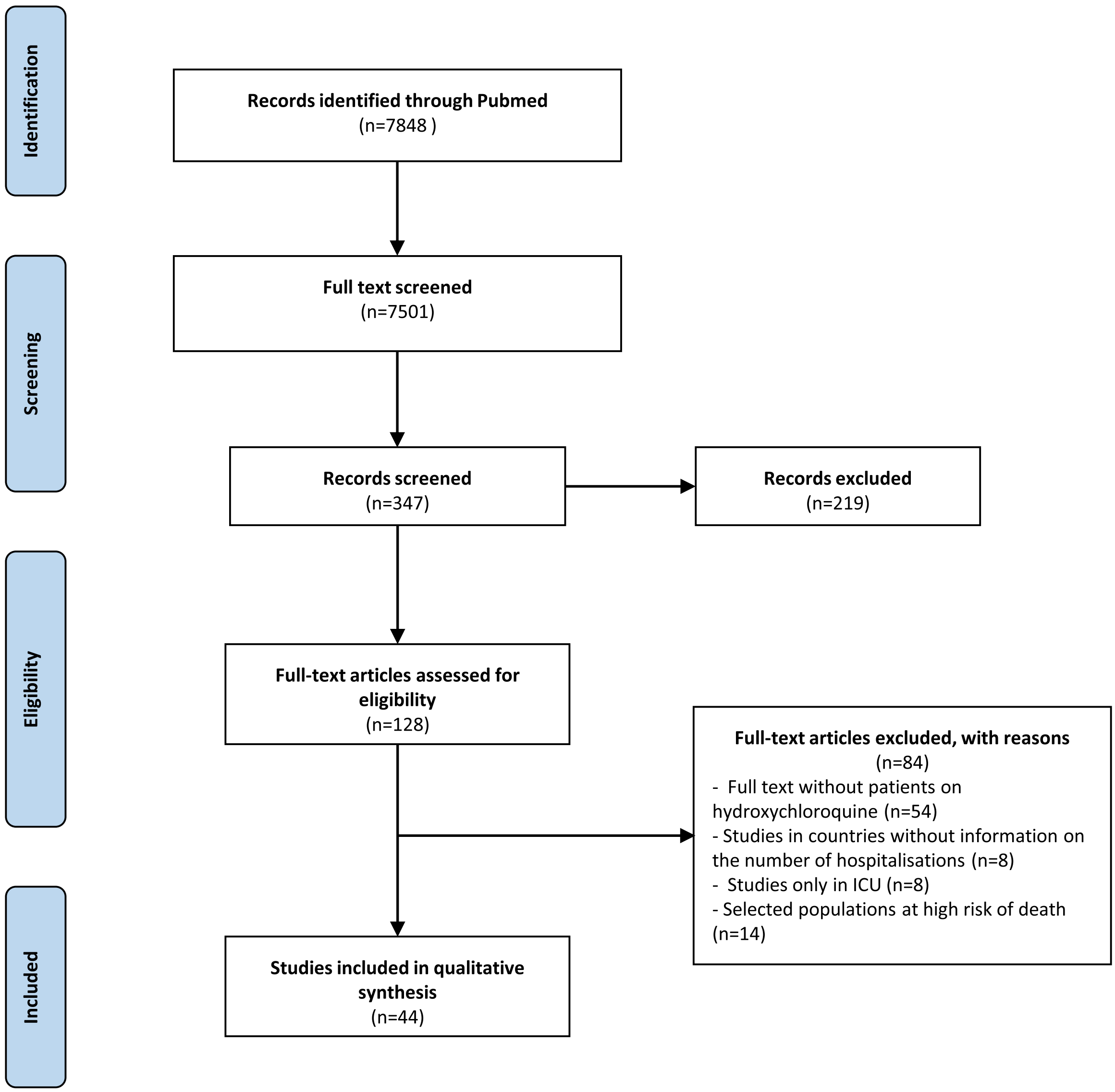

Fig. 1. Flow chart of studies. HCQ: hydroxychloroquine, ICU: intensive care unit.

3.3. Sensitivity analysis

We extracted the mortality rate in hospitalised patients with COVID-19 from the PREMIER database for USA (12.5%) [60], nationwide sources for France (17.4%) [61], Belgium (21.8%) [62], and Spain (29.1%) [63], and regionwide analysis for Turkey (4.5%) [64] and Italy (28.0%) [65].

Using these data for estimates, the median number of HCQ-related deaths in Belgium, Turkey, France, Italy, Spain, and the USA was 240 (range not estimable), 77 (range 75–105), 299 (range not estimable), 2237 (range 1437–2533), 2799 (range 2179–3094) and 7583 (range 1990–9288), respectively. Using median estimates of HCQ use in each country, 13226 in-hospital deaths (range 6211–15530) may be related to HCQ prescription in the six assessed countries.

4. Discussion

The main finding of the present study is that HCQ might have been associated with an excess of 16990 deaths during the first wave of the COVID-19 pandemic in the six countries for which data were available. Given that reliable data on hospitalizations, HCQ use and in-hospital mortality for most countries, these numbers likely represent the tip of the iceberg only thus largely underestimating the number of HCQ-related deaths worldwide. Off-label prescribing may be appropriate when physicians judge they have enough evidence to suggest medication benefit. However, the first series reporting HCQ effect showed limited or no efficacy on mortality reduction [66]. Thus, the expected efficacy might be of modest magnitude at best, similar to other medications in the absence of obvious benefit. As a theoretical example, taking a 15% mortality rate in hospitalised patients and a 30% death reduction related to an effective drug administration, the number needed to treat would be ≈ 20 patients to prevent one death [67]. In other words, administrating off-label drugs to a given patient with COVID-19 outside a randomised study results in a slight individual benefit for them. Conversely, generating high-level evidence from powered and unbiased randomised controlled trials testing promising drugs, following Chalmers' principle to "randomize the first patient", has become increasingly urgent [68,69].

The toxicity of HCQ in patients with COVID-19 is partially due to cardiac side effects, including conduction disorders (ventricular tachycardia or fibrillation, and QT interval prolongation) [70–72]. In the RECOVERY trial, the risk of major cardiac arrhythmia related to HCQ in COVID-19 patients was 8.2% compared to 6.3% in the standard care group, with a 0.4% increased risk of death from cardiac causes [5]. The

Table 1
Characteristics of the included studies.

Study	Country	Prospective design	Consecutive inclusion	Study aim	Start of inclusions	End of inclusions	Study size	Mean age (years)	Men (%)	ICU (%)	All-cause mortality (%)	N. of patients on HCQ	HCQ exposure (%)
Catteau et al. [19]	Belgium	No	No	Treatment	14/03/2020	24/05/2020	8910	NA	55	6	22	4542	51
Kaeuffer et al. [20]	France	Yes	Yes	Prognosis	March 2020	March 2020	1045	66	59	32	11	163	16
Fauvel et al. [21]	France	No	Yes	Prognosis	26/02/2020	20/04/23	1240	64	58	15	12	NA	NA
Bartoletti et al. [37]	Italy	No	No	Treatment	22/02/2020	30/06/2020	513	71	66	23	34	445	87
Fumagalli et al. [36]	Italy	No	Yes	Prognosis	22/02/2020	10/04/2020	516	67	67	NA	23	268	52
Patti et al. [35]	Italy	No	Yes	Prognosis	01/03/2020	12/05/2020	522	NA	59	NA	NA	398 from 456	76
Ameri et al. [34]	Italy	No	Yes	Prognosis	01/03/2020	09/04/2020	689	67	69	NA	24	574	83
Piano et al. [33]	Italy	No	No	Prognosis	22/02/2020	08/04/2020	565	66	63	15	17	412	73
Rinaldi et al. [32]	Italy	Yes	Yes	Prognosis	15/03/2020	30/04/2020	885	NA	67	20	22	811	92
Schiavone et al. [31]	Italy	No	Yes	Prognosis	23/02/2020	01/04/2020	844	63	62	5	22	681	81
Novelli et al. [30]	Italy	No	Yes	Prognosis	23/02/2020	14/03/2020	508	66	72	19	34	332 from 444	65
Mitacchione et al. [29]	Italy	No	Yes	Prognosis	23/02/2020	31/03/2020	842	64	62	5	22	NA	NA
Guaraldia et al. [39]	Italy	No	No	Treatment[a]	21/02/2020	24/03/2020	544	67	66	NA	16	NA	NA
Franco et al. [38]	Italy	Yes	No	Prognosis	01/03/2020	10/05/2020	670	69	69	0	27	263 from 321	39
CORIST [28]	Italy	No	Yes	Treatment	19/02/2020	23/05/2020	3451	NA	62	NA	17	2634	76
Martínez-Sanz et al. [23]	Spain	No	No	Treatment	31/01/2020	23/04/2020	1229	NA	62	7	15	1134	92
Gil-Rodrigo et al. [22]	Spain	Yes	Yes	Prognosis	01/03/2020	30/04/2020	1000	62	56	6	12	698	70
Casas-Rojo et al. [24]	Spain	No	Yes	Prognosis	27/03/2020	30/06/2020	15111	NA	57	8	21	12915 from 15084	85
Gutiérrez-Abejón et al. [25]	Spain	No	Yes	Prognosis	01/03/2020	31/05/2020	7307	NA	57	NA	24	4746	65
Núñez-Gil et al. [27]	Spain	No	Yes	Prognosis	06/03/2020	02/04/2020	914	NA	59	NA	28	752 from 884	82
Pérez-Belmonte et al. [26]	Spain	No	Yes	Prognosis	01/03/2020	19/07/2020	2666	74.9	62	NA	NA	2185	82
Altuntas et al. [16]	Turkey	No	Yes	Prognosis	11/03/2020	29/05/2020	994	NA	55	16	9	712	72
Yigenoglu et al. [17]	Turkey	No	Yes	Prognosis	11/03/2020	22/06/2020	1480	56	54	15	10.3	1049	71
Ozturk et al. [18]	Turkey	No	Yes	Prognosis	17/04/2020	06/05/2020	1210	NA	55	22	14	1173 from 1199	97
Bahl et al. [40]	USA	No	No	Prognosis	01/03/2020	31/03/2020	1461	NA	53	26	22	1073	73
Brar et al. [41]	USA	No	Yes	Prognosis	03/03/2020	15/052020	585	NA	55	NA	22	333	57
Adrish et al. [42]	USA	No	Yes	Prognosis	09/03/2020	18/05/2020	1173	NA	61	NA	33	867	74
Frontera et al. [43]	USA	Yes	No	Prognosis	10/03/2020	20/05/2020	4491	NA	58	22	21	3015	67
Ionescu et al. [44]	USA	No	Yes	Prognosis	13/03/2020	05/05/2020	3480	65	49	18	15	2556	73
Kim et al. [45]	USA	No	Yes	Prognosis	12/03/2020	17/05/2020	510	64	66	68	32	381	75
Rosenberg et al. [46]	USA	No	No	Treatment	15/03/2020	28/03/2020	1438	NA	60	23	20	1006	70

(continued on next page)

Table 1 (*continued*)

Study	Country	Prospective design	Consecutive inclusion	Study aim	Start of inclusions	End of inclusions	Study size	Mean age (years)	Men (%)	ICU (%)	All-cause mortality (%)	N. of patients on HCQ	HCQ exposure (%)
Arshad et al. [47]	USA	No	Yes	Treatment	10/03/2020	02/05/2020	2541	64	51	24	18	1202	47
Magagnoli et al.[48]	USA	No	Yes	Treatment	09/03/2020	29/04/2020	807	~70	96	NA	19	412	50
Kim et al. [49]	USA	No	Yes	Prognosis	01/03/2020	30/05/2020	867	57	55	23	14	222	26
Fried et al. [50]	USA	No	Yes	Prognosis	02/15/2020	20/04/2020	11721	NA	53	20	21	4232	36
Avery et al. [51]	USA	No	Yes	Prognosis	01/03/2020	21/08/2020	2472	NA	52	NA	11	408	17
Keller at al. [58]	USA	NA	NA	Treatment[b]	11/03/2020	13/04/2020	1806	62	47	NA	15	NA	NA
Ho et al.[52]	USA	No	Yes	Prognosis	07/03/2020	05/06/2020	4909	65	57	21	28	3304	67
Li et al.[59]	USA	No	NA	Treatment[a]	12/03/2020	17/06/2020	1938	65	53	26	15	NA	NA
Mikami et al. [53]	USA	No	Yes	Prognosis	13/03/2020	17/04/2020	3708	NA	57	NA	22	2813	76
Laszkowska et al.[54]	USA	No	Yes	Prognosis	11/03/2020	28/04/2020	2804	63	56	NA	19	1383	49
Yeramaneni et al. [55]	USA	No	No	Treatment	11//02/2020	08/05/2020	7158	57	49	NA	10	2529	35
Piazza et al. [56]	USA	No	Yes	Prognosis	13/03/2020	03/04/2020	399[c]	62	57	43	14	279	70
El-Solh et al. [57]	USA	No	Yes	Prognosis	01/01/2020	01/05/2020	1634	69	95	50	29	747	46

HCQ: hydroxychloroquine, UK: United Kingdom, USA: United States of America, N.: number, NA: not applicable, ICU: intensive care unit
[a] tocilizumab
[b] glucocorticoids
[c] from a series including 1114 hospitalised patients and outpatients

increased risk of death from cardiac causes in RECOVERY corresponds to one half of the increase of the all-cause mortality, suggesting the HCQ-related deaths are also related to non-cardiac causes. In a trial conducted in Brazil, testing hydroxychloroquine (HCQ) with or without azithromycin, an increase in hepatic and cardiac side effects, primarily manifesting as the prolongation of the corrected QT interval, was reported [73]. In this trial, the rate of fatal adverse event was 0.4%. The reports of adverse events in the others randomized trials testing HCQ in COVID-19 were scare [74]. In rheumatoid arthritis, the long-term use of HCQ was associated with a higher risk of major adverse cardiovascular events, including myocardial infarction, hospitalisation for heart failure, all-cause and cardiovascular mortality in patients with a history of heart failure [71,72]. The analysis of the European EudraVigilance database also reported the occurrence of HCQ related non-cardiac side effects (in COVID-19 patients, including hepatitis, acute renal failure, hemolytic anemia and rhabdomyolysis [75]. The weight of other adverse events reported in patients treated with HCQ, such as acute eosinophilic pneumonia [76], severe blood disorders such as thrombocytopenia [77], aplastic anemia [77], and agranulocytosis [77], seizures [77], psychiatric disorders [77,78] gastro-intestinal involvement [78,79], and hypoglycaemia [77] is unknown.

In the absence of restriction, the number of expected HCQ-related deaths is likely to be directly related to the promotion of its prescription by scientists, physicians and health agencies. In February and March 2020, the use of this treatment was widely promoted based on preliminary reports suggesting a potential efficacy against COVID-19 [80]. For instance, the use of HCQ markedly increased from mid-March to mid-April 2020 [81,82] in France before a temporary recommendation supporting its use by the State Council was rapidly rejected [83]. Similarly, the Food and Drug Administration (FDA) granted a temporary emergency use authorisation for HCQ on March 28th 2020, which was finally revoked on June 15th 2020 [84]. In India, HCQ was also prescribed as a curative treatment to patients with COVID-19 and as a prophylactic treatment for front-line workers based on public authority guidance [85]. Conversely, the British government promoted HCQ use only within clinical trials, explaining the absence of cohort studies reporting the use of HCQ in the United Kingdom in the present study [86]. Consistently, a cohort of a multinational network showed a wide variation in the use of HCQ between countries, with 85% in Spain, 14% in the USA and less than 2% in China [80]. The rush to administer this treatment caused supply shortages in community pharmacies, forcing the implementation of dispensing restrictions [82]. Finally, the results of observational studies and randomized trials in May and June 2020, respectively, convincingly demonstrated that HCQ was ineffective and led to an increase in adverse events [4,5,12,66,73].

Our study showed a high proportion of prescriptions for HCQ even in countries which have restricted its use [84]. This result argues in favour of tightly regulating access to off-label prescriptions during future pandemics [87]. As an example, the issuance of the emergency use authorization for HCQ by the FDA, which permits distribution of the drug from the national stockpile for the treatment of hospitalized patients with COVID-19, was widely misinterpreted as an FDA approval for this indication [87]. The COVID-19 crisis has led to the implementation of a randomization platform enabling the rapid conduct of clinical trials [3]. Such a structure underscores even less justification for empiricism in off-label prescription. In addition, it is critical that representatives of public authorities should not, on the basis of their personal conviction, promote the prescription of medicines that have not been formally evaluated, thereby falsely raising hopes as to the existence of a solution to a complex health crisis [88–90]. Finally, it is important to bear in mind the risk of extrapolating the treatment effects in one condition to another, where the relevance of intermediate outcome (e.g. viral load) and the putative benefits are overestimated and the undesirable effects downplayed [91–93]. In the context of a new emerging infectious disease, the experience of COVID-19 argues in favour of confining expert advice to contextualising the results of preclinical and clinical studies, rather than generating "new results" from hazardous extrapolation [94].

Our study has some limitations. First, some of the results should be taken with caution, particularly the results obtained in France, Turkey and Belgium. For these countries, data concerning HCQ exposure were

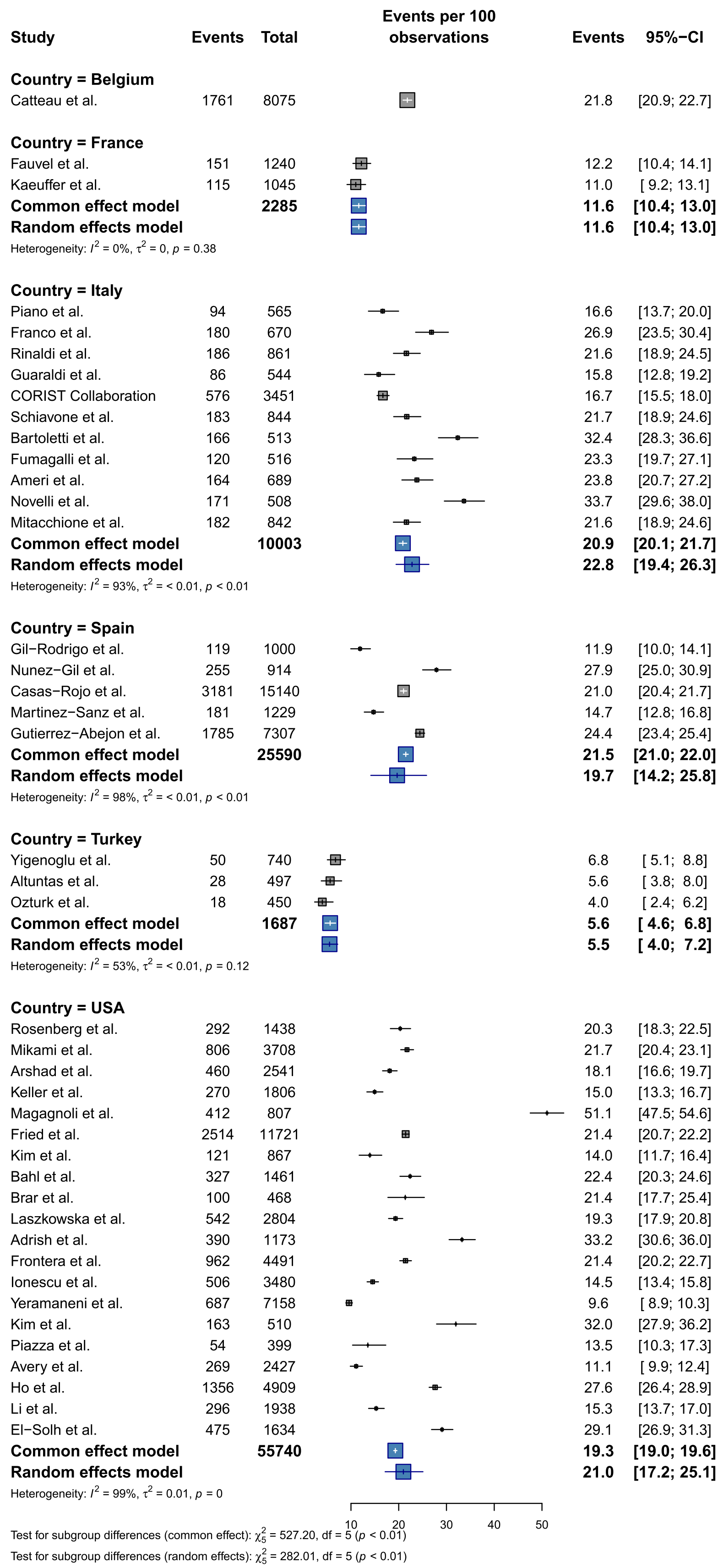

Fig. 2. Meta-analysis of mortality rates according to each country.

Table 2
Mortality induced by hydroxychloroquine by country using the estimate of mortality rate from meta-analysis of including cohorts.

Country	N. of hospitalisations	Rate of prescriptions (range)	N. of hospitalised patients exposed to HCQ (range)	Mortality rate	Odds ratio of treatment mortality	N. of patients who died on treatment (range)	N. of patients' excess mortality by treatment (range)
Belgium	19644	51.0[§]	10018	0.218	1.11	2424	**240**
France	99997	15.6[§]	15600	0.116	1.11	2009	**199**
Italy	89895	80.8 (51.9 - 91.5)	72635 (46656 - 82254)	0.228	1.11	18,383 (11808 - 20817)	**1822** (1170 - 2063)
Spain	104715	83.5 (65.0 - 92.3)	87437 (68065 - 96652)	0.197	1.11	19120 (14884 - 21135)	**1895** (1475 - 2094)
Turkey	21417	73.1 (70.8 - 99.1)	15656 (15163 - 21224)	0.055	1.11	956 (926 - 1296)	**95** (92 - 128)
USA	888037	62.1 (16.3 - 75.9)	551471 (144750-674020)	0.210	1.11	128548 (33741 - 157114)	**12739** (3244 - 15570)

HCQ: hydroxychloroquine, N.: number, USA: United States of America [§] Only one study reported the rate of hydroxychloroquine prescription

Table 3
Mortality induced by hydroxychloroquine by country using the estimate of mortality rate from other sources.

Country	N. of hospitalisations	Rate of prescriptions (range)	N. of hospitalised patients exposed to HCQ (range)	Mortality rate	Odds ratio of treatment mortality	N. of patients who died on treatment (range)	N. of patients' excess mortality by treatment (range)
Belgium	19644	51.0[§]	10018	0.210	1.11	2424	**231**
France	99997	15.6[§]	15600	0.116	1.11	2009	**299**
Italy	89895	80.8 (51.9 - 91.5)	72635 (46656 - 82254)	0.280	1.11	18383 (11808 - 20817)	**2237** (1437 - 2533)
Spain	104715	83.5 (65.0 - 92.3)	87437 (68065 - 96652)	0.291[a]	1.11	19120 (14884 - 21135)	**2799** (2179 - 3094)
Turkey	21417	73.1 (70.8 - 99.1)	15656 (15163 - 21224)	0.045	1.11	956 (926 - 1296)	**77** (75 - 105)
USA	888037	62.1 (16.3 - 75.9)	551471 (144750-674020)	0.125	1.11	119978 (31492 - 146640)	**7583** (1990 - 9268)

HCQ: hydroxychloroquine, N.: number, USA: United States of America [§] Only one study reported the rate of hydroxychloroquine prescription
[a] The study included outpatients.

scarce. As a result, estimates in these countries are more imprecise. Unfortunately, due to the lack of political determination to assess the effect of off-label prescriptions during the COVID-19 crisis, it is unlikely that additional large-scale data will be generated from these countries. Second, the data used were extracted directly from cohort studies. However, a practice study carried out in France showed that HCQ prescription was highly heterogeneous and largely influenced by several factors, the most important being the presence of an established departmental procedure supporting its prescription [95]. Taken together, these results suggest a strong centre effect based, which may have biased the true HCQ exposure. Unfortunately, hospital databases were not available to precisely determine the true HCQ exposure in deceased patients with COVID-19. Third, we estimated the mortality of hospitalised patients using data from published cohorts. Similarly, mortality rates significantly varied across hospitals and regions, which may have been influenced by variable age, sex, comorbidities, ICU capacity, improvement in COVID-19 management, and trust of the population in the national health system and pandemic-related policies [96–98]. This is supported by our sensitivity analysis using national surveillance data from Spain and USA. However, the relative effect of HCQ exposure on outcomes was not modified. Fourth, we did not use all sources of uncertainties related to variables included in the models. We only included variables related to the HCQ treatment effect. Thus, HCQ-related deaths may be considerably over- or under-estimated. Indeed, the 95% confidence interval of the OR of all-cause mortality related to HCQ ranged from 2% to 20%. In other words, our results might be overestimated by a factor 5 (i.e. the actual number of deaths related to HCQ would be ≈3000 deaths) or underestimated by a factor 2 (i.e. the actual number of deaths related to HCQ would be ≈30000 deaths). Thus, the effect of HCQ on mortality was the main source of uncertainty for the proposed estimates. Finally, some estimates could not be calculated due to missing or incomplete information, such as the number of hospitalisations in China, South Korea, Russia and Qatar. The number of deaths related to HCQ worldwide was obviously underestimated because of the lack of studies in regions, such as East Europe, United Kingdom, Germany, Scandinavia, Africa, and South America. Since the number of inhabitants living in the countries included in the present study was ≈ 600 million, we might speculate that the real number of HCQ-induced deaths might be significantly higher given the wide use of HCQ during the first and subsequent waves in numerous countries [85,99,100]. In addition, the number of deceased outpatients exposed to HCQ is unknown. Accordingly, the present results should be viewed as rough estimates only.

In conclusion, the number of HCQ-related deaths is estimated at 16990, even though this number is probably underestimated because of the lack of data from most countries. More importantly, this study illustrates the limitations of treatment-effect extrapolation from chronic to severe conditions without accurate data and the need to produce quickly high-level evidence from RCTs in case of emergent diseases.

Role of the funding source

No funding was received for this study.

Declaration of Competing Interest

No author declared conflict of interest.

Acknowledgement

We thank Pr Michel Cucherat (previously member of Université Claude Bernard Lyon 1, France) for the methodological assistance during design conception. We thank Gaelle Simeon for her editorial assistance.

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